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Original Research

Visualizing mast cell migration to tumor sites using sodium iodide symporter of nuclear medicine reporter gene

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ABSTRACT

Purpose: Owing to the close relationship between mast cells and cancer progression, an imaging technique that can be applied in a clinical setting to explore the biological behavior of mast cells in the tumor microenvironment is needed. In this study, we visualized mast cell migration to lung tumor lesions in live mice using sodium iodide symporter (NIS) as a nuclear medicine reporter gene.

Experimental design: The murine mast cell line MC-9 was infected with retrovirus including NIS, luciferase (as a surrogate marker for NIS), and Thy1.1 to generate MC-9/NFT cells. Radioiodine uptake was measured in MC-9/NFT cells, and an inhibition assay of radioiodine uptake using $KClO_4$ was also performed. Cell proliferation and FcεRI expression was examined in MC-9 and MC-9/NFT cells. The effect of mast cell-conditioned media (CM) on the proliferation of Lewis lung cancer (LLC) cells was examined. The migration level of MC-9/NFT cells was confirmed in the presence of serum-free media (SFM) and CM of cancer cells. After intravenous injection of MC-9/NFT cells into mice with an LLC tumor, I-124 PET/CT and biodistribution analysis was performed.

Results: MC-9/NFT cells exhibited higher radioiodine avidity compared to parental MC-9 cells; this increased radioiodine avidity in MC-9/NFT cells was reduced to basal level by $KClO_4$. Levels of FcεRI expression and cell proliferation were not different in parental MC-9 cell and MC-9/ NFT cells. The CM of MC-9/NFT cells increased cancer cell proliferation relative to that of the SFM. The migration level of MC-9/NFT cells was higher in the CM than the SFM of LLC cells. PET/CT imaging with I-124 clearly showed infiltration of reporter mast cells in lung tumor at 24 h after transfer, which was consistent with the findings of the biodistribution examination.

Conclusion: These findings suggest that the sodium iodide symporter can serve as a reliable nuclear medicine reporter gene for non-invasively imaging the biological activity of mast cells in mice with lung tumors. Visualizing mast cells in the tumor microenvironment via a nuclear medicine reporter gene would provide valuable insights into their biological functions.

Introduction

Mast cells (MCs) are predominantly present in lesion areas with environment contact, which include the mucous membranes, airways, skin, and intestines [1]. They act as important immune cells in various inflammatory reactions such as anaphylaxis, asthma, and atopic dermatitis. Recently, several studies have shown that MCs infiltrate cancer lesions through chemokine gradients, thereby promoting cancer

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cell proliferation [2–6]. Based on these reasons, many researchers have explored the biological role of mast cells in tumor micro-environment to develop new agents that can effectively modulate the mast cell involvement. However, deciphering their involvement in tumor progression in complex biological systems *in vivo* via traditional methods, including immunohistology, flow cytometry, and western blotting analysis, is difficult. Therefore, a noninvasive approach should be adopted to determine the biological implications of mast cells in tumor-bearing hosts.

Molecular imaging using reporter genes has been applied to noninvasively and sensitively track various cells, including neuronal cells, cancer cells, and immune effector cells in living organisms [7–9]. Among the various reporter genes, the sodium iodide symporter has been identified as an attractive nuclear medicine reporter gene with the potential to be translated into clinical situations [10]. Several studies have demonstrated the effectiveness of NIS reporter gene imaging for the visualization of various immune cells, such as lymphocytes, macrophages, and dendritic cells, via positron emission tomography and single photon emission computed tomography in combination with computed tomography [11–16]. Although the potential of the NIS reporter gene as an immune cell tracker has been described, no reports have demonstrated the feasibility of NIS reporter-mediated imaging for monitoring the migration of mast cells to various diseases, such as cancer, inflammation, and metabolic syndrome.

Herein, we attempted to explore the feasibility of NIS reporter gene imaging for visualizing the migration of mast cell into lung tumor lesions in living mice. MC-9 cells were established using a retroviral system to simultaneously express NIS, luciferase, and Thy1.1. We evaluated the effects of the NIS reporter gene expression on mast cell function by analyzing cell proliferation and phenotypic marker expression. Finally, PET/CT imaging with an I-124 PET radiotracer as an NIS substrate was performed to assess the migration of infused reporter mast cells to lung tumor lesions in living mice.

Materials and methods

Detailed information regarding materials and methods has been described in supporting information.

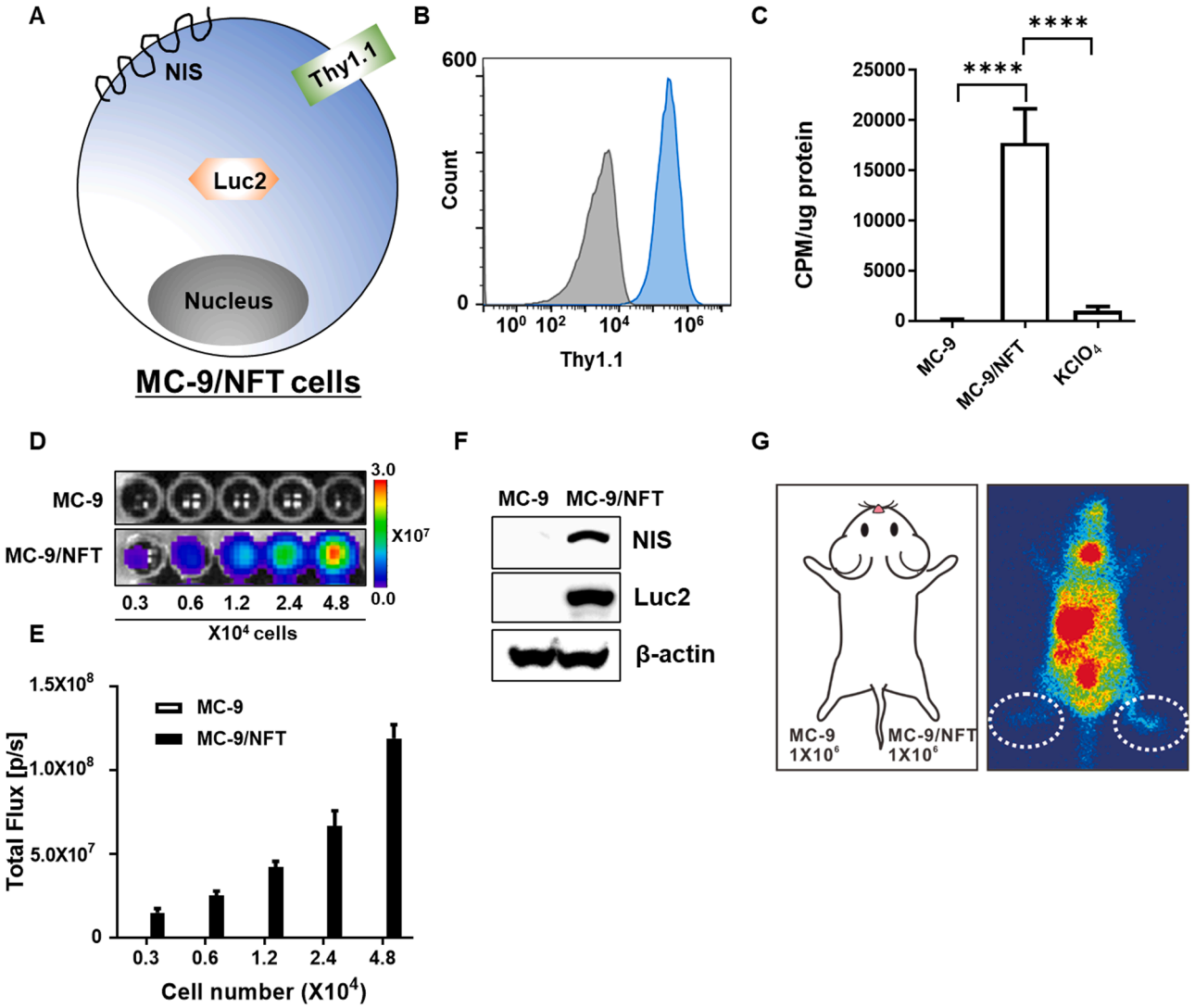

Fig. 1. Establishment of the mast cells expressing NIS gene. (A) Animation showing MC-9 cells co-expressing NIS, luc2, and *Thy1.1* genes called as a MC-9/NFT cells. (B) FACS analysis of MC-9/NFT cells. Cells were stained with either anti-Thy1.1 or isotype antibodies. (gray): isotype control, (blue) anti-Thy1.1 antibody-labeled cells. (C) Radioiodine uptake in MC-9 and MC-9/NFT cells and inhibition study with $KClO_4$. (D) *In vitro* BLI of MC-9/NFT cells according to cell number. (E) Quantification of bioluminescent signals in panel (D). (F) Western blotting showing the expression of NIS and luciferase protein in MC-9/NFT cells. (G) Gamma camera imaging with Tc-99m in mice that received MC-9/NFT cells and MC-9 at right and left paw, respectively. Experiments were performed at least in triplicate and values indicate the mean ± SD.

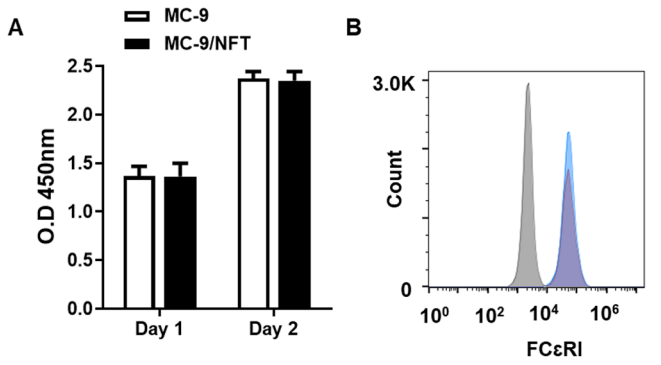

Fig. 2. Effects of NIS reporter gene on mast cell function. (A) Cell proliferation assay in parental MC-9 and MC-9/NFT cells. (B) Level of FcεRIα expression in parental MC-9 and MC-9/NFT cells cells. Gray: Isotype control, blue: MC-9, and purple: MC-9/NFT. Experiments were performed at least in triplicate, and the values indicate the mean ± SD. N.S = not significant.

Results

Establishment of reporter mast cells co-expressing NIS and firefly luciferase genes

MC-9 cells were infected with retrovirus co-expressing NIS, effluc, and Thy1.1 [17]. Subsequently, Thy1.1-expressing cells referred to as MC-9/NFT cells were sorted using previously reported methods [17]. (Fig. 1A). As shown in Fig. 1B, MC-9/NFT cells indicated high expression of Thy1.1, representing NIS and efflux genes, as determined by FACS analysis. As illustrated in Fig. 1C, level of iodide uptake was considerably higher in MC-9/NFT cells than in parental MC-9 cells. Increased radioiodine avidity in MC-9/NFT cells were reduced to basal levels by $KClO_4$ treatment as a selective inhibitor for NIS. Consistently, the luciferase assay showed an increase in bioluminescent signals in a cell number-dependent manner (Fig. 1D and E). Western blotting analysis with anti-NIS and luciferase Abs revealed the expression of NIS and luciferase proteins in MC-9/NFT cells but not in parental MC-9 cells (Fig. 1F). After subcutaneous injection of parental MC-9 cells and MC-9/NFT into respective paws of mice, a gamma camera with Tc-99m as the NIS-selective tracer was used. The gamma camera imaging detected high uptake of Tc-99m in the MC-9/NFT-injected paws but not in the MC-9 cell-injected paws (Fig. 1G).

Effects of NIS gene expression on the function of mast cells

We examined whether the introduction of a reporter gene affects the biological functions of mast cells, such as cell proliferation and phenotypic marker expression. As depicted in Fig. 2A, cell proliferation did not differ between parental MC-9 cells and MC-9/NFT cells. Because MC-9 cells express the FcεRI as a unique phenotype marker of mast cells, we examined its expression level in parental MC-9 cells and MC-9/NFT cells. FACS analysis showed high expression of FcεRI in both cells (Fig. 2B). However, we did not observe a significant difference of its expression in two groups.

Mast cell-mediated increase of cancer cell proliferation

We explored the effects of conditioned media (CM) of reporter mast cells on the proliferation of luciferase expressing lung cancer cells (LLC/luc). As shown in Fig. 3A and B, the CM of MC-9/NFT induced higher

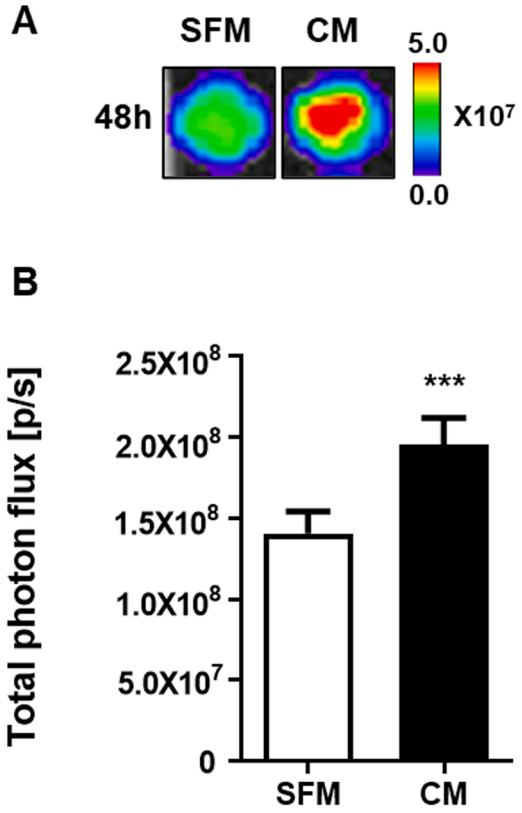

Fig. 3. Enhanced proliferation in LLC cells mediated by mast cell conditioned media. (A) *In vitro* BLI showing the increased proliferation of LLC cells by exposure of CM from mast cells. (B) Quantification of BLI signals in (A) panel. CM from mast cells was added to LLC/effluc cells. SFM was used as the negative control. Experiments were performed at least in triplicate and values indicate the mean ± SD. ***P < 0.001, compared with SFM.

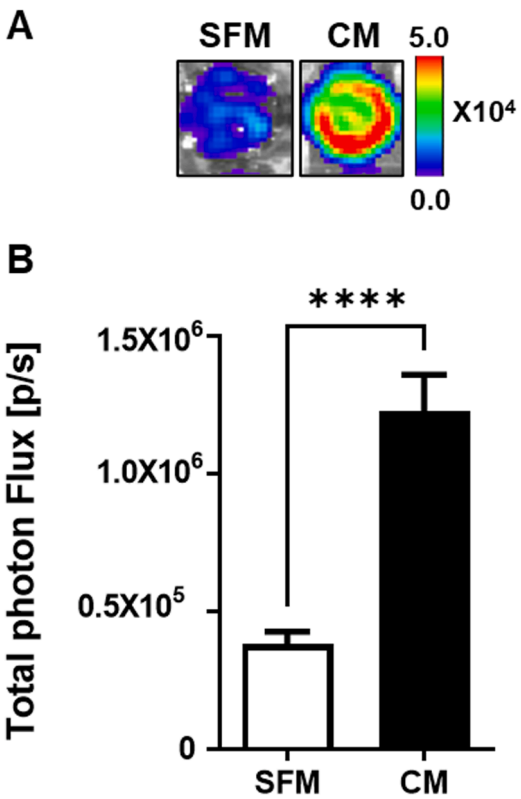

Fig. 4. Enhanced proliferation in LLC cells mediated by mast cell conditioned media. (A) *In vitro* BLI showing the migrated MC-9/NFT cells after exposure to CM derived from LLC cells. SFM or 100% CM from LLC cells was added to the lower chamber. Experiments were performed at least in triplicate and values indicate the mean ± SD. ***P < 0.001, compared with SFM.

proliferation of LLC/luc cells compared the serum-free media (SFM) at 48 h post-treatment, which was evaluated via in vitro bioluminescent imaging.

In vivo imaging of mast cell migration to lung tumor lesion using NIS reporter gene

To investigate the CM effects of Lewis lung cancer cells on reporter mast cell migration, transwell migration was performed. The results of the transwell migration test demonstrated considerably higher luciferase signals in MC-9/NFT cells treated with CM from LLC cells than in those treated with SFM (Fig. 4A and B).

Finally, we investigated whether molecular imaging with the NIS reporter allowed for *in vivo* mast cell tracking in tumor bearing mice, as described in Fig. S1. Briefly, tumor-bearing mice received either efflux-expressing MC-9 cells (MC-9/effluc) [18] or MC-9/NFT cells via retro-orbital injection, followed by I-124 PET/CT imaging and biodistribution examination. As shown in Fig. S2, bioluminescent signals were detected in the tumor lesions of both mice that received either MC-9/effluc cells or MC-9/NFT cells. In the case of I-124 PET/CT imaging, PET quantification analysis with CT-based segmentation revealed intensive radioactive signals in the tumor lesions of mice injected with MC-9/NFT cells (Fig. 5A and B). However, few radioactive signals were observed in the tumor lesions of the mice injected with MC-9/efflux cells. Consistent with the findings of PET/CT imaging, biodistribution analysis revealed higher radioactivity in the tumors of mice injected with MC-9/NFT cells than in those of mice injected with MC-9/effluc cells (Fig. 5C).

Discussion

Understanding the complex involvement of mast cells in the initiation and progression of cancer is important; therefore, a new approach to reveal their various biological actions in the tumor microenvironment of living subjects is urgently needed. Although several researchers have demonstrated the imaging of mast cells in preclinical models using various imaging techniques, it remains difficult to apply this mast cell-imaging approach to clinical situations [19]. Therefore, development of a clinically applicable mast cell imaging technique is required. In this study, we demonstrated the usefulness of the NIS-mediated nuclear medicine imaging approach via I-124 PET/CT imaging for visualizing mast cell recruitment to cancer lesions in living mice.

Inducing stable expression of the reporter gene for effective tracking of immune cells is essential. Thus, many researchers have used retroviral and lentivirus systems for the strong and stable expression of reporter genes in various immune cells [9]. Hence, we also selected a retroviral

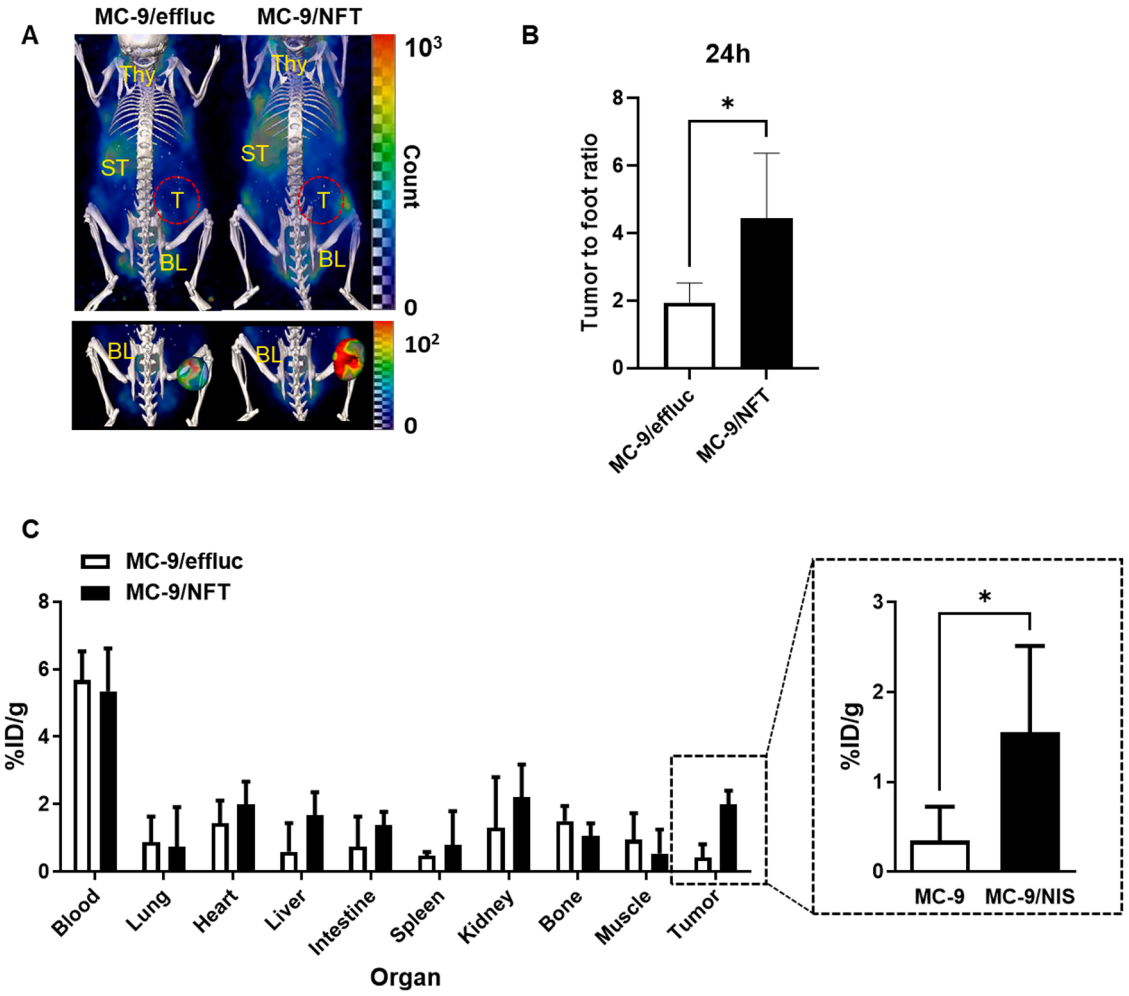

Fig. 5. *In vivo* monitoring of mast cell migration to the tumor lesion using NIS reporter. (A) 3D-reconstructed PET/CT imaging showing the mast cell migration to LLC tumor lesions. Tumor-bearing mice received MC-9/NFT cells via retro-orbital injection, and their migration to the tumor lesions was monitored at 24 h post-transfer. (B) Bar graph showing the tumor to foot ratio. Physiological iodide uptake was observed in the thyroid (T), stomach (ST), and bladder (BL). (C) Biodistribution of infused MC-9/NFT cells in tumor-bearing mice. After PET/CT imaging acquisition, the radioactivity of indicated organs was determined using gamma counter. Experiments were performed at least in duplicate, and values indicate the means ± SD. *P < 0.05, compared with MC-9/effluc.

system co-expressing the NIS, luc2, and Thy1.1 gene [17] developed in previous reports. Luciferase—the most sensitive optical reporter gene—serves as a surrogate marker for NIS reporter genes in *in vivo* imaging studies. Thy1.1 gene can be used to sort NIS-positive cells using a microbead-conjugated Thy1.1 specific antibody and a magnetic separation approach. MC-9 cell of murine mast cell line was selected for this study because it exhibits an IL-3 dependency and high expression of FcεRI and is commonly used in mast cell-related fields [20]. Using our reporter retrovirus system, we successfully introduced the NIS reporter gene into MC-9 cells and enriched the NIS-positive cells by up to approximately 95% by cell sorting. As the overexpression of NIS in mast cells leads to increased radioiodine avidity, we conducted a radioiodine uptake assay in the parental MC-9 cells and MC-9/NFT cells. As expected, we observed a drastic increase in radioiodine uptake in NIS-expressing mast cells (MC-9/NFT cells) but not in parental MC-9 cells. Consistently, NIS expression was confirmed in MC-9/NFT cells but not in parental MC-9 cells by western blotting analysis. Importantly, increased iodine uptake was completely inhibited by $KClO_4$ of the NIS-selective inhibitor, suggesting that an enhanced radioiodine uptake was mediated by NIS expression and its functional activity in MC-9/NFT cells.

The introduction of exogenous reporter gene should not affect the biological activity of mast cells, which include cellular proliferation and phenotype marker expression. The proliferation assay using CCK-8 assay showed no difference in cell proliferation between parental MC-9 cells and MC-9/NFT cells. Mast cells exhibited high FcεRI expression on the cell surface, and its aggregation by external stimuli (neuropeptides and allergen) induces the release of inflammatory mediators [1,2]. FACS analysis with FcεRI-reactive antibody showed the high expression of FcεRI in MC-9 cells and MC-9/NFT cells. However, no difference in gene expression between the two cell types was observed. These results indicate that the exogenous expression of the NIS gene did not elicit any detrimental effects on the mast cells' biological activities.

Mast cells are recruited via various types of chemokine gradients generated by cancer cells, and the infiltrated mast cells in tumor lesion produce many extracellular matrix enzymes and growth factors, which is directly associated with inferior prognosis of cancer patients [2,6]. Consistent with these findings, we observed a greater increase in the migration of reporter mast cells in the conditioned media of LLC cells than in serum-free media. Furthermore, we observed a higher proliferation of LLC cells when treated with conditioned media from MC-9/NFT cells compared with serum-free media.

Several studies have shown that the number of mast cells is higher in cancerous tissues than in normal tissues. Previously, we observed the existence of endogenous mast cells in LLC tumor lesions via toluidine blue staining—an immune-histological technique for the detection of MCs [18]. Therefore, LLC cancer xenografts have been established for the *in vivo* study. MC-9/NFT and enhanced firefly luciferase expressing MC-9 cells (MC-9/effluc as control group) were administered to tumor-bearing mice by retro-orbital injection, followed by optical and PET/CT imaging on day 1 post-transfer. For PET/CT imaging in combination with NIS, I-124 of positron-emitting iodine isotope was used [21]. Prior to I-124 PET/CT imaging, bioluminescent imaging was performed because of the ease and sensitivity of imaging techniques for detecting a few populations of migrated cells in tumor lesions. Bioluminescent signals were detected in tumor lesions of mice receiving MC-9/NFT and MC-9/effluc cells. Importantly, higher radioactivity was observed in the tumor lesions of MC-9/NFT cells than in MC-9/efflux cells on I-124 PET/CT imaging. Consistent with *in vivo* PET/CT findings, biodistribution examination showed higher radioactivity in the tumor lesions of mice that received MC-9/NFT cells than in those that received MC-9/efflux cells. These findings suggest that NIS reporter gene imaging is a feasible method for monitoring of mast cell migration in tumor-bearing mice.

Conclusion

We successfully tracked mast cell migration to tumor sites in living mice via nuclear medicine imaging of the NIS gene. We believe that the mast cells expressing NIS may provide a new approach for exploring the biological role of mast cells in tumor microenvironment in preclinical models. Subsequent investigations should prioritize the *in vivo* imaging of primary mast cell migration utilizing NIS reporter genes in a range of cancer models, as well as models of allergy and inflammation.

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CRediT authorship contribution statement

Seul-Gi Oh: Conceptualization, Project administration, Investigation, Writing – review & editing, Writing – original draft. **Jun Young Choi:** Conceptualization, Project administration, Investigation, Writing – review & editing, Writing – original draft. **Jae-Eon Lee:** Conceptualization, Project administration, Investigation, Writing – review & editing, Writing – original draft. **SoYeon Jeon:** Conceptualization, Project administration, Investigation, Writing – review & editing, Writing – original draft. **Bo-Ra Lee:** Formal analysis, Data curation, Writing – review & editing, Writing – original draft. **Kwang Hee Son:** Formal analysis, Data curation, Writing – review & editing, Writing – original draft. **Sang Bong Lee:** Formal analysis, Data curation, Writing – review & editing, Writing – original draft. **Beum-Soo An:** Writing – review & editing, Writing – original draft. **Dae Youn Hwang:** Validation, Writing – review & editing, Writing – original draft. **Seong-Jang Kim:** Validation, Writing – review & editing, Writing – original draft. **Ki-Tae Ha:** Validation, Writing – review & editing, Writing – original draft. **Jaetae Lee:** Writing – review & editing, Writing – original draft. **Yong Hyun Jeon:** Supervision, Investigation, Writing – review & editing, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] M. Schemann, M. Camilleri, Functions and imaging of mast cell and neural axis of the gut, Gastroenterology 144 (4) (2013) 698–704, e4.
[2] K. Khazaie, N.R. Blatner, M.W. Khan, F. Gounari, E. Gounaris, K. Dennis, A. Bonertz, F.N. Tsai, M.J. Strouch, E. Cheon, The significant role of mast cells in cancer, Cancer and Metastasis Rev. 30 (1) (2011) 45–60.
[3] T.C. Theoharides, Mast cells and pancreatic cancer, N. Engl. J. Med. 358 (17) (2008) 1860.
[4] R. Melillo, V. Guarino, E. Avilla, M. Galdiero, F. Liotti, N. Prevete, F. Rossi, F. Basolo, C. Ugolini, A. De Paulis, Mast cells have a protumorigenic role in human thyroid cancer, Oncogene 29 (47) (2010) 6203–6215.
[5] A. Derakhshani, F. Vahidian, M. Alihasanzadeh, A. Mokhtarzadeh, P.L. Nezhad, B. Baradaran, Mast cells: a double-edged sword in cancer, Immunol. Lett. 209 (2019) 28–35.
[6] D. Ribatti, Mast cells as therapeutic target in cancer, Eur. J. Pharmacol. 778 (2016) 152–157.
[7] R. Weissleder, Molecular imaging in cancer, Science 312 (5777) (2006) 1168–1171.

[8] E. Gu, W.Y. Chen, J. Gu, P. Burridge, J.C. Wu, Molecular imaging of stem cells: tracking survival, biodistribution, tumorigenicity, and immunogenicity, Theranostics 2 (4) (2012) 335.
[9] M.F. Kircher, S.S. Gambhir, J. Grimm, Noninvasive cell-tracking methods, Nat. Rev. Clin. Oncol. 8 (11) (2011) 677–688.
[10] P. Acton, R. Zhou, Imaging reporter genes for cell tracking with PET and SPECT, Q. J. Nucl. Med. Mol. Imag. 49 (4) (2005) 349.
[11] S.B. Lee, H.W. Lee, H. Lee, Y.H. Jeon, S.W. Lee, B.C. Ahn, J. Lee, S.Y. Jeong, Tracking dendritic cell migration into lymph nodes by using a novel PET probe 18 F-tetrafluoroborate for sodium/iodide symporter, EJNMMI Res. 7 (2017) 1–9.
[12] J.H. Seo, Y.H. Jeon, Y.J. Lee, G.S. Yoon, D.I. Won, J.H. Ha, S.Y. Jeong, S.W. Lee, B. C. Ahn, J. Lee, Trafficking macrophage migration using reporter gene imaging with human sodium iodide symporter in animal models of inflammation, J. Nucl. Med. 51 (10) (2010) 1637–1643.
[13] C. Ashmore-Harris, M. Iafrate, A. Saleem, G.O. Fruhwirth, Non-invasive reporter gene imaging of cell therapies, including T cells and stem cells, Mol.Ther. 28 (6) (2020) 1392–1416.
[14] E. Sharif-Paghaleh, K. Sunassee, R. Tavaré, K. Ratnasothy, A. Koers, N. Ali, R. Alhabbab, P.J. Blower, R.I. Lechler, L.A. Smyth, *In vivo* SPECT reporter gene imaging of regulatory T cells, PLOS One 6 (10) (2011) e25857.
[15] A. Volpe, C. Lang, L. Lim, F. Man, E. Kurtys, C. Ashmore-Harris, P. Johnson, E. Skourti, R.T. de Rosales, G.O. Fruhwirth, Spatiotemporal PET imaging reveals differences in CAR-T tumor retention in triple-negative breast cancer models, Mol. Ther. 28 (10) (2020) 2271–2285.
[16] H.W. Lee, S.Y. Yoon, T.D. Singh, Y.J. Choi, H.J. Lee, J.Y. Park, S.Y. Jeong, S.W. Lee, J.H. Ha, B.C. Ahn, Tracking of dendritic cell migration into lymph nodes using molecular imaging with sodium iodide symporter and enhanced firefly luciferase genes, Sci. Rep. 5 (1) (2015) 9865.
[17] S.B. Ahn, S.B. Lee, T.D. Singh, S.J. Cho, S.K. Kim, I.K. Lee, S.Y. Jeong, B.C. Ahn, J. Lee, S.W. Lee, Multimodality imaging of bone marrow–derived dendritic cell migration and antitumor immunity, Transl. Oncol. 10 (2) (2017) 262–270.
[18] S.G. Oh, X. Li, H.W. Lee, T.D. Singh, S.B. Lee, H.D. Ji, G. Yoon, S.J. Cho, I.K. Lee, S. Y. Jeong, Non-invasive visualization of mast cell recruitment and its effects in lung cancer by optical reporter gene imaging and glucose metabolism monitoring, Biomaterials 112 (2017) 192–203.
[19] S. Tikoo, N. Barki, R. Jain, N.S. Zulkhernain, S. Buhner, M. Schemann, W. Weninger, Imaging of mast cells, Immunol. Rev. 282 (1) (2018) 58–72.
[20] T. Ishizuka, A. Oshiba, N. Sakata, N. Terada, G.L. Johnson, E.W. Gelfand, Aggregation of the FcεRI on mast cells stimulates c-Jun amino-terminal kinase activity: a response inhibited by wortmannin, J. Biol. Chem. 271 (22) (1996) 12762–12766.
[21] B.C. Ahn, Sodium iodide symporter for nuclear molecular imaging and gene therapy: from bedside to bench and back, Theranostics 2 (4) (2012) 392.